

CRYSTAL-CLOUDY, CRYSTAL-CLEAR

Roald Hoffmann

We are remembered by our exaggerations. So at a recent reunion of my former research-group members, several recalled my saying “When you see a standard deviation in an x-ray crystal structure, multiply it by pi [π , 3.141...], or if the structure is done by friends, by e [2.718...].”

I was talking about structures of molecules—details of their geometry, also of a particularly fruitful way to gain knowledge of these structures. And of the error estimates in such studies.

There is no more basic enterprise in chemistry than the determination of the geometrical structure of a molecule. Such a determination, when it is well done, ends speculation and provides us with the starting point for understanding every physical, chemical and biological property of the molecule. Indeed, the chemical sciences (only modestly imperialistic, I take them to range from materials science through molecular biology) are what they are today largely as the result of careful structure determination. We’d be still waiting in ignorance if we believed the hype of various microscopies. A few very accurate structures have come to us through ingenious use of electron diffraction and various spectroscopies. But the vast majority of what we know about shapes and metric detail of molecules and extended materials derives from studies of the diffraction of x rays by single crystals of molecules, a technique popularly called “x-ray crystallography.”

The Intermolecular Shuffle

The molecules in a crystal are not in a vacuum. They are in the solid state because of intermolecular forces—variously called van der Waals, dispersion or crystal-packing forces. Easy to parameterize in approximate calculations, excruciatingly hard to compute *a priori*, the intermolecular forces are weakly attractive at long distances, but have a repulsive hard core. The tiny attractions add up and make the molecules condense. And, because molecules are to a degree flexible, the intermolec-

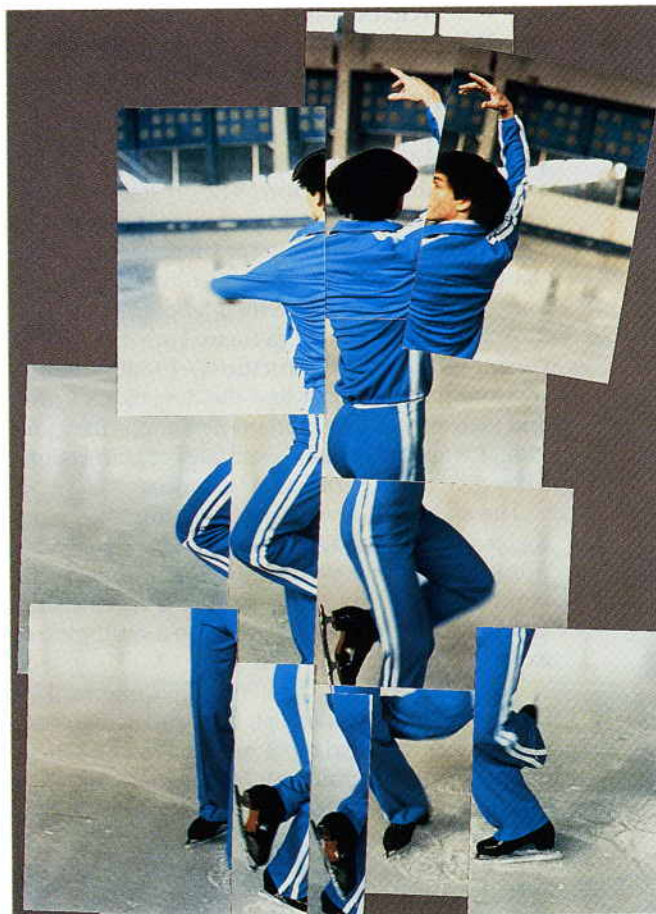


Figure 1. *The Skater*, David Hockney’s 1982 photocollage captures the essence of motions of people and molecules.

ular forces affect distances and angles in every molecule in the crystal by a small step dance of pushing and pulling on each other. Something is gained overall—otherwise the crystal would not form. But crystallization may take place at the cost of a small change in a bond distance or an angle relative to the unencumbered gas-phase structure. There are no tugs on a molecule sailing through outer space.

These weak intermolecular forces are behind my skeptical exclamation. Let me elaborate, and then tell a story of how the very same forces that cause the substantial chemical variance in the structure of a molecule can be used to get valuable

Roald Hoffmann is professor of chemistry at Cornell University. He is the coauthor, with Shira Leibowitz Schmidt, of *Old Wine, New Flasks: Reflections on Science and Jewish Tradition*, recently published by W. H. Freeman. Address: Baker Laboratory, Cornell University, Ithaca, NY 14853-1301.

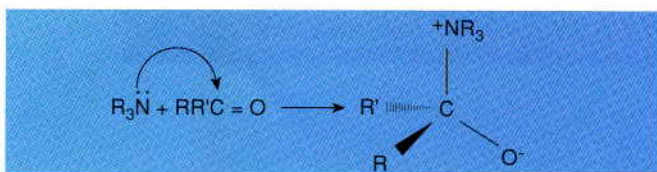


Figure 2. Nucleophilic addition of an amine to a carbonyl group.

information about chemical dynamics, namely the motion of molecules in the course of reaction. Indeed, there is an anniversary to mark—it is nearly 25 years since a pair of landmark papers showed us, with astonishing clarity, that this was possible.

What Crystal Structures Tell

Crystallographic studies are usually done very carefully, although sufficient mistakes of a certain basic type (so-called space-group assignment) are made to provoke one distinguished crystallographer to publish a dreaded article per year replete with his colleague's errors. The crystal structures are carried out by people perhaps more aware of systematic and random error (that "standard deviation") than almost any subculture of our science. So why do I malign their labors?

Actually I don't malign them. I am a voracious consumer of crystal structures—I value them, I treasure them. It's just that the deviations I need and love are not the standard deviations they provide. I want "chemical" estimates of uncertainty: They give me experimental variances.

The standard deviation of a geometrical parameter in a crystallographic structure determination—be it a unit-cell coordinate, a distance, a bond angle—is the square root of a variance, the latter usually denoted σ^2 owing to a multitude of experimental uncertainties.

These are accounted for usually quite well by the careful experimentalist, though I wonder today—when the variances are spewed out in an inking by a computer—whether they are really given as much serious consideration as to origins as they were decades ago.

In my years of molecular voyeurism, I saw the crystal structures get better, and the standard deviations sink, for good data sets to the 0.002 angstrom (\AA) [$1 \text{ \AA} = 10^{-8}$ centimeters] level for organic-molecule distances. But it was also clear to me that $\pm 0.002 \text{ \AA}$ made no *chemical* sense. For I saw in some of the structures (technically those with several molecules in the asymmetric unit) molecules that were chemically identical yet whose relevant matching distances or angles differed by much more than the listed standard deviations, because of the intermolecular forces at play. In fact after a while I began to look for these cases. Or to get an estimate of a chemical standard deviation I focused on the part of the crystal structure that was least interesting—that phenyl group in a triphenylphosphine ligand (hundreds of them, and they should be very much alike). And I saw big deviations.

So that's the reason for my flippant π and e factor. What I also record here is a missed opportunity on

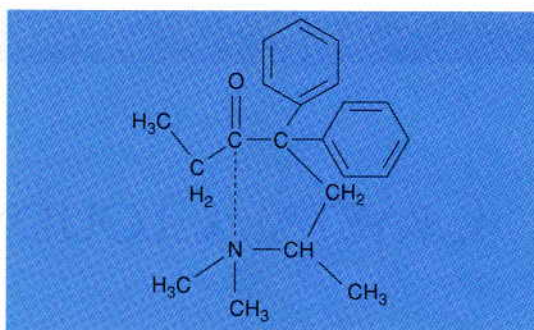


Figure 3. Structure of methadone.

my part—the information was on hand, and I just quipped. Antonio Martín and A. Guy Orpen of the University of Bristol in the United Kingdom did what needed to be done (and didn't get their idea from me, either). In what is certain to be a classic paper, in 1996 they showed from an examination of thousands of metal-complex structures that crystal-packing forces cause standard deviations of the order of 0.01 to 0.02 \AA in ligand distances. So, as it turns out, my π was too conservative!

Snapshots Along the Way

The very same crystal-packing forces, which in a given crystal structure make for more chemical uncertainty than the standard deviations lull you into believing, also teach us so much more than what we imagined we could learn from a static structure. For a group of structures, judiciously chosen, can reveal the geometric changes that a flexible molecule undergoes and even the course of atomic motions in reaction.

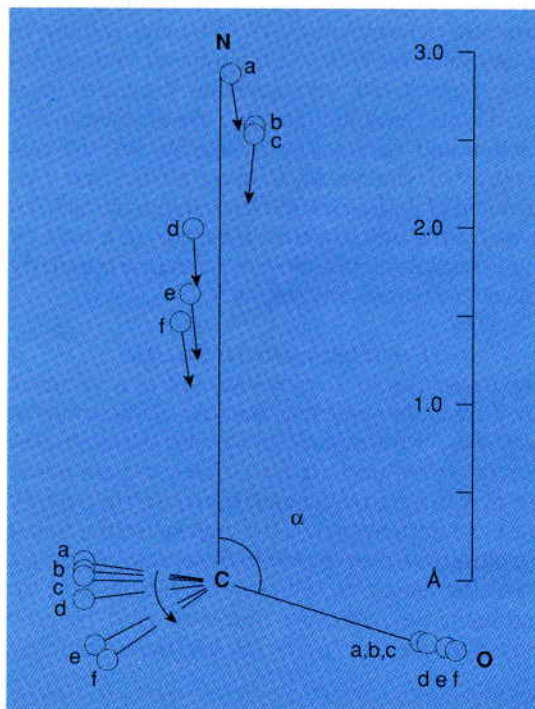


Figure 4. Plot (atom positions on the CO plane) of six crystal structures tracing out the reaction pathway for addition of an amine to a carbonyl. (From Bürgi, Dunitz and Shefter, 1973.)

